IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA UK LIMITED, IPR PHARMACEUTICALS, INC., and SHIONOGI SEIYAKU KABUSHIKI KAISHA, Plaintiffs, v. WATSON LABORATORIES, INC. (NV), Defendant.	Civil Action No. 10-915-LPS

PLAINTIFFS' POST-TRIAL BRIEF

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TABLE OF ABBREVIATIONS

"Arrow"	Arrow Group of companies, including Cobalt
"AstraZeneca"	AstraZeneca UK Limited and IPR Pharmaceuticals, Inc.
"AZD"	AstraZeneca's Demonstrative Exhibit
"Cobalt"	Cobalt Laboratories, Inc. and Cobalt Pharmaceuticals, Inc.
"D.I. __"	Docket number in Civ. No. 10-915-LPS
"DMF"	Drug Master File
"DTX-__"	Defendant's Trial Exhibit
"Egis"	Egis Pharmaceuticals PLC
"EPO"	European Patent Office
"FDA"	U.S. Food and Drug Administration
"HDL"	High Density Lipoprotein
"LDL"	Low Density Lipoprotein
"NDA"	New Drug Application
"Plaintiffs"	AstraZeneca UK Limited, IPR Pharmaceuticals, Inc., and Shionogi Seiyaku Kabushiki Kaisha
"PPFF"	Plaintiffs' Proposed Findings of Fact
"PTO"	U.S. Patent and Trademark Office
"PTX-__"	Plaintiffs' Trial Exhibit
"Shionogi"	Shionogi Seiyaku Kabushiki Kaisha
"The '314 Patent"	United States Patent No. RE37,314
"Tr. xx:yy-zz"	Trial Transcript, page xx, lines yy-zz.
"UFF"	Undisputed Findings of Fact
"Watson"	Watson Laboratories, Inc. (NV)

I. INTRODUCTION

The Court tried this patent infringement action from December 12-19, 2012. The sole issue remaining is infringement of the '314 patent by Watson's proposed rosuvastatin zinc salt under the doctrine of equivalents.

The evidence unambiguously proved that the zinc metal ion in Watson's rosuvastatin compound performs substantially the same function, in substantially the same way, to provide substantially the same result as the metal ions in the rosuvastatin salts that are literally claimed in the '314 patent. Indeed, Watson contended before the FDA (and did not argue differently at trial) that it need not separately test the safety and efficacy of its rosuvastatin zinc product *precisely because* of the similarity it bore to Plaintiffs' rosuvastatin calcium product squarely within the scope of the '314 patent claims. Thus, Watson proposes to do precisely what the doctrine of equivalents was intended in equity and fairness to prevent—usurp the value of the patented invention while making only insubstantial changes. (§ II.A.)

Plaintiffs' patent claims are directed to rosuvastatin in the form of a "non-toxic, pharmaceutically acceptable salt," which the Court held was defined by a statement in the patent text that a similar term "refers to" alkali metal ion, alkaline earth metal ion, and ammonium ion. But the fact that the use of zinc to form the salt was not included in the disclosure or literally claimed in the patent does not excuse Watson's infringement. The Supreme Court and the Federal Circuit have established as a general rule that the doctrine of equivalents extends its protection to undisclosed and unclaimed equivalents. Quite tellingly, Watson does not argue that any specific exception to this general rule applies to this case, and at closing argument counsel for Watson conceded that there is no case directly on point in support of its position. Watson merely cobbles together extracts from various exceptions to the general rule mandating infringement, points to the text of the '314 patent and speculative boilerplate disclosures in other

patents, and argues that it would somehow be unfair to find in AstraZeneca's and Shionogi's favor. But the analysis of the evidence and the law leads to only one conclusion – that there is no legal, factual, or equitable basis for eliminating Plaintiffs' access to the doctrine of equivalents. (§ II.B.)

The evidence overwhelmingly establishes that the '314 patent text did not convey to a person of ordinary skill in the art as of its 1991 effective filing date that the inventors had considered rosuvastatin zinc and chose to exclude it from their invention. Any argument to the contrary ignores the scientific realities associated with the discovery of new statins in 1991. At that time, the *only* non-toxic metal salts of statins that had actually been synthesized used the metal cations described in the '314 patent. *Nobody* had actually synthesized a zinc salt of *any* statin in 1991. Even 14 years later, when Egis made its rosuvastatin zinc salt in 2005, Egis itself asserted to the PTO that it was novel. Although by 2010 rosuvastatin zinc was known to be an equivalent, there is no evidence that any scientist ever even considered the possibility of a *rosuvastatin* zinc salt from 1991 until the idea was mentioned in a Chinese patent application filed 13 years later in 2004. The '314 patent's disclosure of suitable salt-forming metal ions was not narrow (as Watson contends) but rather was entirely reasonable and appropriate under the circumstances. That disclosure reflected precisely what a medicinal discovery chemist working in the real world of statin research actually would have considered using for development of a statin metal salt in 1991. (§§ II.B.3-4.)

Watson attempts to re-write history and have the Court apply to 1991 what was known only later. Speaking from the 21st century, where rosuvastatin zinc is known, Watson has selectively resurrected the actions of some patent lawyers for a few companies who adopted and repeated then-speculative "boilerplate" disclosures that included zinc (along with toxic

aluminum ions) as a potential salt-forming possibility for *other statins*. Those over-inclusive speculations of a few patent lawyers, however, do not establish rosuvastatin zinc as a real, viable alternative to medicinal discovery chemists of ordinary skill in the art of statins in 1991. There is simply no contemporaneous evidence that zinc was genuinely viewed as a real, viable alternative *to statin scientists* at the relevant time period. (§ II.B.4.)

The doctrine of equivalents is fundamentally equitable in nature. It exists to preserve the incentive for innovation by protecting inventors from those making insubstantial variations that avoid the literal scope of the claims. The instant case cries out for its application. Shionogi in its patent did what it was supposed to do—it claimed and disclosed the classes of salts it had made and did nothing unusual or improper with those claims during reissue. Watson was not misled by any good faith reliance on the language of the patent claims—Watson's licensor and predecessor knew early on that there was a substantial risk that this zinc product might be viewed as an infringing equivalent to Shionogi's patent. The invention of the '314 patent, which was found valid by Judge Farnan and affirmed by the Federal Circuit, was and is medically important and worthy of broad protection under the doctrine of equivalents. Watson has added nothing of value to that discovery. Instead, Watson attempts to gain a windfall by adopting a variation of the patented invention that only became known to scientists as a viable option more than a decade after the '314 patent application was filed and that happens to avoid the literal scope of its claims. The doctrine of equivalents exists for this very situation—to protect innovators, like Plaintiffs, from those, like Watson, who make insubstantial variations that avoid the literal scope of the claims. (§§ II.C.)

For reasons set forth more fully below, the evidence, law, and equity warrant a judgment of infringement. The operative facts are set forth in connection with the ensuing argument, in the

Joint Statement of Undisputed Facts (UFF), and in Plaintiffs' Proposed Findings of Fact (PPFF), filed concurrently herewith.

II. THE LAW AND EVIDENCE SUPPORT A FINDING OF INFRINGEMENT

The Supreme Court in *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 607 (1950), recognized the doctrine of equivalents because "to permit imitation of a patented invention which does not copy every literal detail would be to convert the protection of the patent grant into a hollow and useless thing."

The Supreme Court held that "a patentee *may invoke this doctrine* to proceed against the producer of a device if it performs substantially the same function in substantially the same way to obtain the same result." *Id*. at 608 (emphasis added). This doctrine results in a finding of infringement here because (a) Plaintiffs established such infringement by a preponderance of the evidence, and (b) there are no legal or evidentiary bases on which the Court should reject application of the doctrine of equivalents.

A. Plaintiffs Proved by a Preponderance of the Evidence that Watson's Rosuvastatin Zinc Is Equivalent in Fact to the Salts Literally Claimed in the '314 Patent

Watson infringed claims 6, 7, and 8 of the '314 patent pursuant to 35 U.S.C. § 271(e)(2)(A) by submitting its NDA No. 202172 to the FDA to commercially market and sell its product before expiration of the '314 patent. (*See* UFF at ¶ 21.) Infringement was established under the doctrine of equivalents because Watson's rosuvastatin zinc contains elements that are identical or equivalent to the elements of those claims, as shown below.

1. The Applicable Legal Standard

The inquiry into whether a potential substitute is equivalent under the doctrine of equivalents must be made from the perspective of one of ordinary skill in the art at the time of the infringement—here, at the time Watson filed its NDA in 2010. *Warner-Jenkinson Co. v.*

Hilton Davis Chem. Co., 520 U.S. 17, 37 (1997). Plaintiffs bear the burden to prove infringement by a mere preponderance of the evidence. *See Lemelson v. United States*, 752 F.2d 1538, 1547 (Fed. Cir. 1985). Specifically, Plaintiffs must show by a preponderance of the evidence that the accused product contains "elements identical or equivalent to each claimed element of the patented invention." *Warner-Jenkinson*, 520 U.S. at 40. Whether the inquiry is framed in terms of "insubstantial differences" or in terms of "substantially the same function, way, and result" is not important, so long as the analysis addresses "the essential inquiry [of whether] the accused product or process contain[s] elements identical or equivalent to each claimed element of the patented invention." *Id*.

2. The '314 Patent Specification and Claims Provide the Framework for the Infringement Analysis Under the Doctrine of Equivalents

"What constitutes equivalency must be determined against *the context of the patent*, the prior art, and the particular circumstances of the case." *Graver Tank*, 339 U.S. at 609 (emphasis added); *see also Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1359 (Fed. Cir. 2005). "Consideration must be given to *the purpose for which an ingredient is used in a patent*, the qualities it has when combined with the other ingredients, and the function which it is intended to perform." *Graver Tank*, 339 U.S. at 609 (emphasis added).

The specification of the '314 patent discloses novel pyrimidine compounds, including rosuvastatin, and makes clear that "[t]he compounds of the present invention inhibit the HMG-CoA reductase, which plays a main role in the synthesis of cholesterol, and subsequently they suppress the biosynthesis of cholesterol." (Tr. at 242:20-243:10; PTX-1227 at col. 1, ll. 29-34.) Moreover, the patent specification explains that the claimed compounds, including their salts, achieve their intended biological activity when they are dissolved and placed into solution. (Tr. at 995:9-996:19; PTX-1227 at col. 14, l. 10-col. 15, l. 10 ("A solution . . . of sodium salt of the

test compound dissolved in potassium phosphate buffer is added to . . . the mixture [of rat liver microsome].").)

In this context, the therapeutically active portion of the claimed rosuvastatin salts is the negatively-charged rosuvastatin anion liberated upon dissolution of the salt. (Tr. at 238:10-239:6; 239:17-22, 591:23-592:18, 596:4-21.) The function performed by the positively-charged metal cations in the claimed compounds is to provide the active rosuvastatin anion in an electrically neutral, soluble form. (*Id*.) The way the claimed metal cations do so is by forming a non-toxic, pharmaceutically-acceptable, soluble salt with the rosuvastatin anion. (*Id*.) The result of forming such a salt in the context of the claimed invention is that the claimed salts dissolve to deliver the rosuvastatin anion in solution into the body of a patient, where it inhibits the synthesis of cholesterol. (Tr. at 242:20-243:10; PTX-1227; *see also* PPFF at ¶¶ 78-82.)

It is not disputed that Watson's product contains an identical rosuvastatin anion and differs from the claimed salts only in the substitution of a zinc cation for the cations literally encompassed by the patent claims. (Tr. at 237:11-238:9.) The evidence available in 2010 confirms that this difference is insubstantial. (*See* PPFF at ¶¶ 75-107, 113, 130, 144-148.)

a. Admissions in Watson's Rosuvastatin Zinc FDA Submission Establish Equivalence

Watson based its regulatory submission on the similarities of its rosuvastatin zinc to the rosuvastatin calcium embodiment claimed in the '314 patent, which is the active ingredient in Crestor®. (PTX-17 at W1452.) Specific admissions in Watson's NDA demonstrate the insubstantiality of the substitution it has made with respect to the specific properties of the rosuvastatin invention disclosed and claimed in the '314 patent. Watson admits that (1) its rosuvastatin zinc contains the active rosuvastatin anion (PTX-317 at W6295-96), (2) its rosuvastatin zinc is a powder (PTX-17 at W1451), (3) its rosuvastatin zinc is orally administered

(PTX-16 at W1272), (4) its rosuvastatin zinc is dissolved and achieves its therapeutic effect in solution within the patient's body (PTX-18 at W1596-97), and (5) the solubility of its rosuvastatin zinc is similar to the solubility of rosuvastatin calcium under a variety of conditions (Tr. at 245:23-247:15; PTX-17 at W1451; PTX-317 at W6297; PTX-732 at AZW530022-23; *see also* PTX-1641-S).

Additionally, Watson's NDA admits that the rosuvastatin zinc tablet products "perform similarly to the reference drug product, Crestor® Tablets" and that "[t]he two products exhibit very similar *in vitro* [dissolution] behavior . . . ." (Tr. at 252:14-253:14; PTX-18 at W1596-97; PTX-1293 at W940.) Watson also admits that its drug substance has "similar solubility properties to rosuvastatin calcium" (Tr. at 245:9-22; PTX-17 at W1451), and Watson concedes that its rosuvastatin zinc tablets are designed to be "bioequivalent" to Crestor® reference tablets (PTX-18 at W1595).

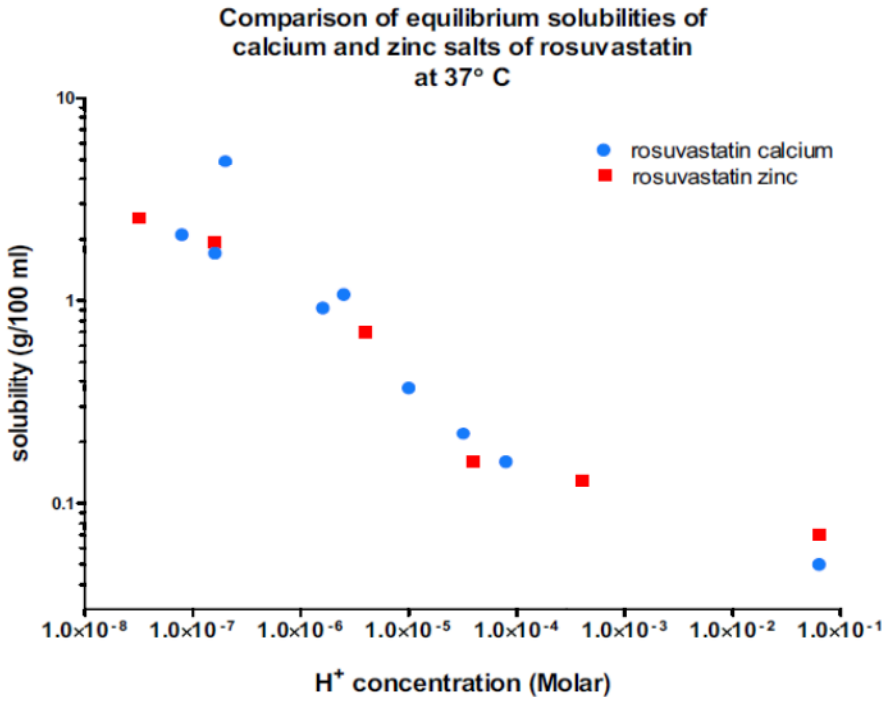
Significantly, Watson relied on these admitted similarities to rosuvastatin calcium to avoid conducting expensive and time-consuming preclinical and clinical studies to prove the safety and efficacy of its proposed rosuvastatin zinc product. (Tr. at 265:21-267:8; PTX-17 at W1452; PTX-334; PTX-1254; PTX-1294.) Watson convinced the FDA that the products were so similar that Plaintiffs' expansive clinical studies of rosuvastatin *calcium* demonstrate the safety and efficacy of Watson's rosuvastatin *zinc*. (PTX-1254 at W1418-19; PTX-1294.)

b. Solubility of Rosuvastatin Zinc and the Claimed Salts Is Insubstantially Different

Solubility data relates to whether a given salt form can provide the active ingredient in solution. It is undisputed that when a soluble rosuvastatin salt goes into solution, the anion and cation separate (Tr. at 238:10-16), and once separated, the original cation has virtually no association with the original rosuvastatin anion (Tr. at 241:5-12). In the body, after the salt

dissolves, the original cation has a negligible effect on the total cation concentration. (Tr. at 238:17-241:4, 241:13-242:7.) Furthermore, it is the rosuvastatin anion that binds to HMG-CoA reductase, and the cation used in salt formation does not participate in that interaction. (Tr. at 238:10-239:6, 241:5-12; PTX-734 at 1161, Figure 1.)

Dr. Sawchuk, an expert in pharmacokinetics and pharmacodynamics, reviewed data indicating that the solubilities of rosuvastatin zinc and rosuvastatin calcium are insubstantially different over a broad pH range. (Tr. at 245:23-247:15; PTX-317 at W6297; PTX-732 at AZW530022-23.) That data is summarized in PTX-1641-S as follows:



Dr. Sawchuk testified further that such differences as there may be in solubility are insubstantial. (Tr. at 247:11-15, 250:9-11.) He testified that both rosuvastatin zinc and rosuvastatin calcium are classified as "highly soluble" under the Biopharmaceutics Classification System ("BCS"), while their shared rosuvastatin anion has low permeability, leading to (1) their placement in BCS Class 3 and (2) the conclusion that their use would result in substantially the same permeability of the rosuvastatin anion across the gastrointestinal membrane. (Tr. at

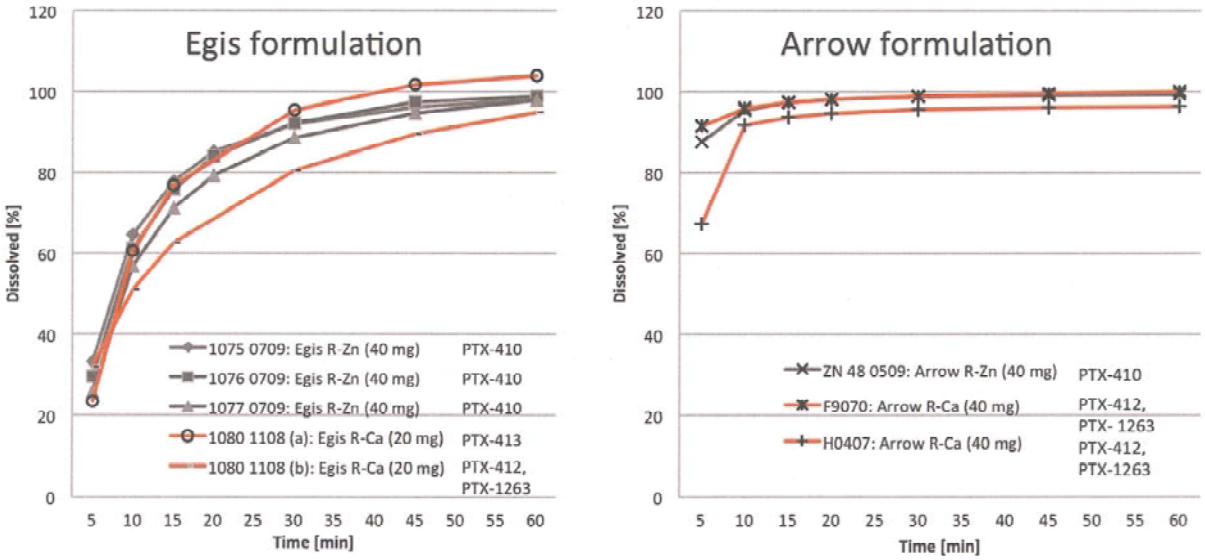
232:8-19; 248:21-251:8; PTX-317 at W6297; PTX-732 at AZW530022-23; PTX-1641-S.) That is so because intestinal permeability—not solubility—is the rate-limiting step for uptake into the circulation for rosuvastatin and other BCS Class 3 drugs. (Tr. at 232:8-19; 250:5-251:5; PPFF at ¶ 97.) Thus, minor differences in solubility result in only insubstantial changes in the delivery of the active rosuvastatin anion within the body.

Additionally, the solubility of rosuvastatin sodium, potassium, lithium, and magnesium salts are comparable to or greater than the solubility of the calcium and zinc salts of rosuvastatin, reflecting insubstantial differences in *in vivo* performance between the use of zinc and the use of these other claimed ions to make rosuvastatin salts. (Tr. at 251:9-252:13.) Significantly, Dr. Morris acknowledged that solubility is a key property described in the '314 patent, but did not allege there were any substantial differences in the solubilities of rosuvastatin zinc and the claimed salts. (Tr. at 907:15-908:18, 995:9-996:19.)

i. Tablet Dissolution Is Insubstantially Different

Dr. Sawchuk concluded that any differences in dissolution between Watson's proposed rosuvastatin zinc product and commercial rosuvastatin calcium formulations (Crestor®) within the literal scope of the '314 patent claims are insubstantial. (Tr. at 252:14-255:13; PTX-1293 at W935.) Watson admits that the dissolution profiles of its rosuvastatin zinc tablets compared to claimed rosuvastatin calcium formulations (Crestor®) demonstrate that there is "no significant difference between the dissolution profile of all strengths of [rosuvastatin zinc] tablets manufactured by EGIS Pharmaceuticals PLC and the reference [rosuvastatin calcium] drug product originated from [the U.S.]. The two products exhibit very similar *in vitro* behavior: over 85% of the active was released after only 15 minutes in all strengths of both products." (Tr. at 252:14-255:13; PTX-1293 at W940.)

Moreover, Dr. Sawchuk reviewed dissolution data from rosuvastatin zinc and calcium salts in two otherwise identical formulations—one from Arrow and one from Egis. The comparative data are reproduced below:



(Tr. at 255:14-258:13; PTX-1640-S; *see also* AZD-3.14.)

With regard to the Egis formulation, the rosuvastatin zinc dissolution curves fall between the two rosuvastatin calcium curves. With regard to the Arrow formulation, the rosuvastatin zinc curve lies substantially on top of one of the rosuvastatin calcium curves and in close alignment with the other rosuvastatin calcium curve. Based on these comparisons, Dr. Sawchuk concluded that the specific cation incorporated in the formulation did not affect dissolution, and to the extent there are any alleged differences, these are also insubstantial. (Tr. at 255:14-258:13; *see also* AZD-3.14.)

ii. *In Vivo* Similarities Confirm Equivalence

The pharmacokinetic profiles of Watson's proposed rosuvastatin zinc product and claimed rosuvastatin calcium embodied in Crestor® products, in both fasting and fed studies, are virtually identical to one another. (Tr. at 259:2-261:13; PTX-1292-A at W8247, W8297;

PTX-1323-A at W6829, W6880.) In fact, Watson admitted to the FDA that its rosuvastatin zinc tablets are bioequivalent to Crestor® tablets, and concluded that its rosuvastatin zinc tablets will have a "similar safety and tolerability profile and provide the same clinical efficacy as Crestor®." (PTX-1254 at W1419.)

Based on the *in vitro* and *in vivo* data that he reviewed, Dr. Sawchuk concluded that the use of zinc in a rosuvastatin salt in Watson's product is insubstantially different from the use of calcium, sodium, and the other claimed cations in the rosuvastatin salts of claims 6-8 of the '314 patent. (Tr. at 234:6-235:2, 250:12-252:13, 258:6-13, 259:2-260:10.) Notably, Watson did not put forth a competing expert to dispute any of Dr. Sawchuk's opinions.

3. Any Differences in Other Properties Are Insubstantial

The '314 patent specification contains no description of properties such as physical stability, chemical stability, and hygroscopicity. (Tr. at 373:1-22, 994:11-995:1, 997:1-17.) Accordingly, reference to these properties in assessing equivalency is not pertinent to the equivalence analysis. As discussed below, however, the evidence demonstrated that any differences between the physical and chemical properties of Watson's rosuvastatin zinc and various preparations of rosuvastatin calcium and other claimed rosuvastatin salts are insubstantial.

a. Differences in Physical Form Are Only Insubstantial

The claims of the '314 patent do not require any particular physical form, and the specification describes the exemplified salts as either "powdery crystals" (Example 1) or "powdery" (Example 7). (PTX-1227 at col. 11, ll. 19-23, col. 13, l. 65 - col. 14, l. 1.) With regard to physical form, rosuvastatin zinc and rosuvastatin calcium can each be made in amorphous or crystalline forms. When made as crystalline salts, both zinc and calcium salts can

form crystalline hydrates (i.e., crystal forms containing water). (PTX-729 at AZW620007; PTX-730 at W185, W808.)

The ability to form crystalline salts of rosuvastatin is not unique to rosuvastatin zinc. In addition to calcium, AstraZeneca made crystalline salts with potassium, lithium, magnesium, and ammonium cations. (Tr. at 193:9-195:3; PTX-564; *see also* AZD-2.01.) Moreover, the '314 patent discloses that Shionogi made a crystalline sodium salt of rosuvastatin. (PTX-1227 at col. 11, ll. 19-23; *see also* PTX-636-T.) Therefore, the physical form of the rosuvastatin zinc in Watson's proposed product is insubstantially different from salts literally covered by the patent claims.

b. Differences in Physical Stability Are Only Insubstantial

The physical stability of rosuvastatin zinc in Watson's proposed product is no different than that of salts within the literal scope of the claims of the '314 patent. Like the rosuvastatin calcium crystalline hydrate, a salt form literally claimed, the crystalline material in Watson's rosuvastatin zinc active pharmaceutical ingredient ("API") converts to the amorphous form upon loss of water. (Tr. at 385:4-20; PTX-549 at AZW1012158; PTX-729 at AZW620008; PTX-730 at W186, W188; *see also* PPFF at ¶ 122.) According to the Egis DMF, the rosuvastatin zinc API begins to lose water around 22° C, and the water loss is complete by approximately 77° C. (Tr. at 386:2-387:18; PTX-730 at W186, W188.) Due to its tendency to lose water, the rosuvastatin zinc API must be dried carefully at low temperature (not more than (NMT) 30° C) to maintain its physical form. (Tr. at 387:19-388:22; PTX-20 at W145435; PTX-730 at W808.)

The crystalline hydrate form of rosuvastatin calcium had the same problem. It also carried the potential risk of conversion to an amorphous form upon the loss of water. (Tr. at 173:20-174:15, 178:11-181:13; PTX-549 at AZW1012161; PTX-729 at AZW620008.) But unlike rosuvastatin zinc, which showed some conversion to the amorphous form after only 16

hours at 50° C, AstraZeneca's rosuvastatin calcium crystalline hydrate showed no conversion after four weeks at 50° C. (Tr. at 1012:12-20; PTX-20 at W145432; PTX-547 at AZW1012183; PTX-548 at AZW1012170-72.) Nonetheless, the risk of conversion to an amorphous form at drying temperatures was the reason that a crystalline calcium salt was not adopted for commercial development by AstraZeneca. (PTX-729 at AZW620008.) Amorphous rosuvastatin calcium is physically stable, showing no tendency to convert to a crystalline form. (*Id*.) AstraZeneca chose to develop the amorphous form commercially. (*Id*.)

Watson attempts to divert attention from the substantial similarity of its proposed product by pointing out that AstraZeneca investigated non-calcium salts of rosuvastatin, allegedly due to "sub-optimal properties" of amorphous rosuvastatin calcium. AstraZeneca's continuing research into alternative salt work evidences no failure or shortcoming of its amorphous Crestor® product, evidences no substantial difference between rosuvastatin zinc in Watson's product and those salts literally claimed in the '314 patent, and is wholly unrelated to the equivalence issue presented here. (*See* PPFF at ¶¶ 139-142, 150-152.)

Beyond the foregoing, the evidence established that the risk of conversion to an amorphous form shared by crystalline rosuvastatin calcium and Watson's crystalline rosuvastatin zinc made such salt forms even less "optimal" for commercial development than amorphous rosuvastatin calcium. Watson cannot avoid infringement by adoption of an inferior equivalent. *See*, *e.g.*, *Wahpeton Canvas Co., Inc. v. Frontier, Inc.*, 870 F.2d 1546, 1548 n.2 (Fed. Cir. 1989); *Laitram Corp. v. Cambridge Wire Cloth Co.*, 863 F.2d 855, 859 (Fed. Cir. 1988).

c. Differences in Chemical Stability Are Only Insubstantial

The chemical stability and impurity profile of a rosuvastatin salt are affected by the process by which it is manufactured, and not by the cation used to form the salt. (Tr. at 402:13-23, 409:21-410:8, 499:7-23, 1029:17-22; PTX-469-T at W0185072; PTX-729 at

AZW620378.) Accordingly, Watson's arguments based on stability and impurity profiles miss the mark, because they are not dependent on the equivalent in question.

Nevertheless, the evidence showed that the impurity profile of rosuvastatin zinc is insubstantially different from the impurity profiles of the rosuvastatin salts within the literal scope of the claims. For example, the AstraZeneca rosuvastatin calcium 2010 API specification has a lower total impurity limit than the rosuvastatin zinc specification (NMT 0.9% v. NMT 1.00%, respectively). (PTX-432 at W21; PTX-1326 at AZW1017212-13; *see also* AZD-4.14.) Watson's expert, Dr. Morris, did not consider the 2010 specification for AstraZeneca's rosuvastatin calcium API before making his conclusions. (Tr. at 1023:17-1024:7.) Notably, the FDA approved AstraZeneca's original rosuvastatin calcium API, tentatively approved Watson's rosuvastatin calcium API, and tentatively approved Watson's rosuvastatin zinc API, all of which have minor variations in their impurity profiles (PTX-322 at W124065-66; PTX-432 at W21; PTX-1326 at AZW1017212-13; *see also* AZD-4.14), further demonstrating that any differences in impurity profiles are insubstantial and do not affect the clinical outcomes produced by the rosuvastatin anion.

The evidence of actual measured impurity values of various rosuvastatin calcium APIs versus the proposed rosuvastatin zinc API, clearly establishes that the zinc salt is only insubstantially different. (Tr. at 409:8-410:8; *see also* AZD-4.15.) While Watson focuses much attention on the "B2" impurity, neither AstraZeneca's current rosuvastatin calcium API nor Watson's own rosuvastatin calcium API has any detectable B2 impurity. (PTX-322 at W124065-66; PTX-1326 at AZW1017242; *see also* AZD-4.15.) Indeed, many of the other salts within the scope of the claims similarly have no detectable B2 impurity. (Tr. at 405:7-406:9; PTX-600 at AZW1005381-82, AZW1005384-85.) While the level the "lactone" impurity may

be slightly higher for Watson's rosuvastatin zinc and the level of the B2 impurity may be slightly higher for some preparations of the salts literally claimed, the differences are all well within the range deemed approvable as safe by the FDA. (Tr. at 1027:18-1024:16.) Accordingly, the evidence shows that there is no substantial difference, let alone superiority, associated with the rosuvastatin zinc impurity profile.

Similarly, there is no evidence of any substantial difference in stability. Although Watson's expert, Dr. Morris asserted that the claimed rosuvastatin calcium requires a stabilizer when formulated (and that Watson's rosuvastatin zinc does not), that assertion is contradicted by Watson's own NDA. The pharmaceutical development report filed as part of Watson's NDA shows that Egis tested rosuvastatin calcium in a formulation with and without a stabilizer, and concluded that a stabilizer was not required. (Tr. at 406:11-408:10; PTX-1462 at W170965-67.)

d. Differences in Hygroscopicity and Water Content Are Only Insubstantial

Dr. Morris also alleged that differences in water-uptake or hygroscopicity between rosuvastatin zinc and the claimed salts are substantial. Yet, the evidence established that all rosuvastatin salts are susceptible to degradation when exposed to moisture, heat, and light. (Tr. at 658:3-22; PTX-18 at W1599; PTX-1462 at W170964.) For this reason, both Watson's and AstraZeneca's products are packaged to protect them from these influences, whereby alleged differences in hygroscopicity are simply unimportant. (Tr. at 392:18-394:21, 396:12-398:6, 1037:12-1039:21; PTX-16 at W1320; PTX-729 at AZW619963, AZW620378; PTX-730 at W118-121, W144.)

Both Watson's and AstraZeneca's rosuvastatin salts are hygroscopic. AstraZeneca's NDA for Crestor® describes rosuvastatin calcium as hygroscopic, but explains that the hygroscopicity has no adverse impact on the stability of the drug substance except at extreme

conditions. The Egis DMF describes rosuvastatin zinc API as "slightly hygroscopic" and notes that there was significant moisture absorption, and that rosuvastatin zinc is "highly susceptible to degradation when exposed to moisture and light." (Tr. at 394:22-396:11; PTX-18 at W1599; PTX-729 at AZW620377; PTX-730 at W183.)

The water content specifications in Watson's rosuvastatin zinc NDA and AstraZeneca's rosuvastatin calcium NDA are substantially the same. The NDAs specify that Watson's rosuvastatin zinc API must contain from 6-8% water, while AstraZeneca's rosuvastatin calcium API must contain no more than 6% water. (PTX-16 at W1316, 1349; PTX-729 at AZW620080; PTX-733 at AZW530125; *see also* PPFF at ¶ 128.) The NDAs further specify Watson's rosuvastatin zinc tablets must contain no more than 7% water, and AstraZeneca's rosuvastatin calcium tablets contain no more than 5.5% water. (*Id*.)

Dr. Morris suggests that AstraZeneca's rosuvastatin calcium API picks up more water than Watson's rosuvastatin zinc. (Tr. at 932:2-935:11.) However, Watson's rosuvastatin zinc product already contained 6% water before the test began, while rosuvastatin calcium starts out with a much lower water content. (Tr. at 1033:6-1034:24.)

More significantly, the alleged differences in hygroscopicity are immaterial because they have no practical effect on the packaging and handling of the material. In fact, Watson's rosuvastatin zinc API and AstraZeneca's rosuvastatin calcium API both have packaging that protects from gain or loss of moisture (PTX-16 at W1320; PTX-729 at AZW619963), and both tablets must be protected from the atmosphere (Tr. at 1037:12-1038:2). Any differences in hygroscopicity and water content are, therefore, insubstantial in the context of the claimed invention. (Tr. at 392:18-394:21, 396:12-398:6.)

e. Differences Between Calcium Chemistry and Zinc Chemistry Are Insubstantial in the Context of the Claimed Invention

Both zinc and calcium in their metallic form have two valence electrons that contribute to the chemistry of the atoms in the context of rosuvastatin salts. (Tr. at 593:18-23, 595:2-5.) Both zinc and calcium form ions with a +2 charge, resulting in salts of rosuvastatin that have two rosuvastatin anions and one metal cation. (Tr. at 592:5-18, 596:11-14, 625:22-626:20; *see also* Tr. at 237:18-238:9, 627:3-10 (regarding other literally claimed cations).) Data available in 2010 establishes that rosuvastatin zinc is sufficiently soluble to be classified in BCS Class 3, as are the calcium and other metal salts of rosuvastatin within the literal scope of the '314 patent claims. (Tr. at 248:7-249:14, 250:5-251:5, 251:9-252:1; *see also* PTX-1641-S; PPFF at ¶¶ 97-98.) Rosuvastatin calcium has been approved as non-toxic and safe by the FDA, and rosuvastatin zinc has been tentatively approved as non-toxic and safe by the FDA. (Tr. at 1028:13-1029:2.) Thus, with respect to the properties relevant to the equivalency analysis in this case, the evidence reveals only insubstantial differences arising from the use of zinc in comparison to the metal ions literally claimed in the '314 patent.

Unlike Dr. Roush, Watson's expert Dr. Brittain performed his analysis of calcium, magnesium, and zinc chemistry divorced from the context of the '314 patent and from rosuvastatin salts. Dr. Brittain's expert report did not mention the word rosuvastatin, and he admittedly did not consider the '314 patent. (Tr. at 1105:23-1106:8.) He made no attempt to compare the use of zinc in a rosuvastatin salt to the use for that purpose of cations recited in the '314 patent. (*Id.*) Despite noting differences between the zinc atom and alkaline earth metal atoms, he provided no analysis of rosuvastatin salts containing those metal cations and failed to show that any of his comparisons are relevant to the chemistry of the cations in the context of a rosuvastatin salt. (*Id.*) Accordingly, Dr. Brittain's opinions are wholly divorced from context

and unrelated to the question of whether the use of zinc to form a rosuvastatin salt would have been recognized in 2010 as insubstantially different from the use of the literally claimed cations to form the rosuvastatin salts claimed in the '314 patent.

B. There Are No Legal or Evidentiary Bases on Which the Court Should Reject Application of the Doctrine of Equivalents

Watson's contentions that its otherwise clear infringement should be excused all turn on Shionogi's statement in the '314 patent that the term cation capable of forming a non-toxic pharmaceutically acceptable salt "refers to" alkali metal ions, alkaline earth metal ions, and ammonium ion. This language, as the Court has construed it, simply means that the patent did not disclose and does not literally claim other metal salts, including zinc. The law is clear in this regard that the doctrine of equivalents is still available to prevent use of undisclosed and unclaimed equivalents. Accordingly, Watson tries to turn this statement into something it is not by contending (1) that the salt disclosure is so exceptionally narrow that it evinces a conscious consideration and exclusion of zinc, (2) that the use of zinc salts of statins was so notoriously well-known and foreseeable that failure to mention zinc also evinces such a considered exclusion, and (3) that Shionogi was required to disclose and claim the salts more broadly than they had actually been made, by use of words like "includes," for example, in order to have any broader exclusive rights.

The evidence, however, is strongly to the contrary. The disclosed classes of salts were in fact broad, not narrow, encompassing all of the types of non-toxic statin metal salts that had ever been synthesized prior to 1991. Zinc was not well known and foreseeable as a real, practical alternative. Not only were there no internal medicines sold as zinc salts, but there were no publications indicating that anybody had ever synthesized a statin zinc salt by 1991. Indeed, the evidence is clear that statin salt formation was unpredictable in 1991 and that attempting to

disclose and claim untested classes of salts would have exposed Shionogi to even more allegations of invalidity for lack of an enabling disclosure for those untested salts than it already faced from Watson and Egis in this action. The law does not mandate such a Catch-22, under which untested embodiments must be literally claimed or protected not at all.

The overwhelming weight of the evidence is that no statin scientist, not at Shionogi, not at AstraZeneca, and not anywhere else, ever gave the slightest consideration to the possibility of a rosuvastatin zinc salt for more than a decade after the '314 patent application was filed. Not surprisingly, therefore, none of the traditional circumstances that might defeat resort to the doctrine of equivalents is present here. There is no express or implied disavowal, no prosecution history estoppel, no violation of the "All-Limitations" rule, and no attempt to recapture unclaimed disclosure, as more fully set forth below.

1. The Doctrine of Equivalents Applies to Undisclosed and Unclaimed Equivalents

Watson's principal legal position reduces to the contention that because the patent specification does not disclose rosuvastatin zinc, and because the patent claims have been construed as not literally encompassing rosuvastatin zinc, access to the doctrine of equivalents should be foreclosed. The contention ignores the well-settled law of the doctrine of equivalents.

a. The Doctrine Extends to Undisclosed Equivalents

The fact that the alleged equivalent in this case is *not disclosed* in the patent specification cannot alone bar access to the doctrine of equivalents. The doctrine almost always involves embodiments of the invention that are *not disclosed* in the patent specification. *See*, *e.g., Pozen Inc. v. Par Pharm., Inc.*, 696 F.3d 1151, 1170-72 (Fed. Cir. 2012) (holding equivalence between dissolution percentage of accused embodiment and claimed dissolution percentages, despite former being outside range disclosed in specification); *Abraxis Bioscience, Inc. v. Mayne*

Pharma (USA) Inc., 467 F.3d 1370, 1376-77, 1379-82 (Fed. Cir. 2006) (holding equivalence between accused calcium trisodium DTPA and claimed disodium edetate, despite former not being disclosed in specification). *See also Warner-Jenkinson*, 520 U.S. at 37 (rejecting argument that "equivalents must . . . be actually disclosed in the patent in order for such equivalents to infringe upon the patent"). Indeed, where an embodiment of the invention is disclosed in the specification but not ever claimed, the law may impose a constructive abandonment or dedication to the public of that subject matter. *Johnson & Johnston Assocs., Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054-55 (Fed. Cir. 2002) (en banc); *Maxwell v. J. Baker, Inc.*, 86 F.3d 1098, 1106-08 (Fed. Cir. 1996).

Shionogi did nothing more and nothing less than what it was supposed to do. In filing its original patent application and in stating that the term pharmaceutically acceptable salts "refers to" alkali and alkaline earth metal salts, Shionogi stated what the invention it had actually made *was*. If simply stating what the invention *is* always operated as a statement of what the invention *is not*, such a legal doctrine would always bar access to the doctrine of equivalents whenever the alleged equivalent is not disclosed in the specification, which the Supreme Court has clearly stated is not the law.

It cannot be overemphasized that the structure of the original application text here did *not* reflect amendment to narrow a previously presented broader disclosure of the invention. That text was filed together as a unitary whole and never did disclose the useable salts any more broadly than it does today. The reissue did not impact the text at issue in this case. As the Supreme Court noted in *Warner-Jenkinson*, 520 U.S. at 31, the inclusion of limiting phrases in the original application is "very different" from later narrowing of the scope of the invention. Estoppels arise only from the latter. (*See* § II.B.5.a., *infra*.)

b. The Doctrine Applies to Unclaimed Equivalents

The doctrine of equivalents *always* involves alleged infringement by an embodiment of the invention *outside* the literal scope of the claims. Otherwise, the issue would be one of literal infringement. Thus, the fact that the patentee has not literally claimed the alleged equivalent cannot alone bar access to the doctrine, since such a rule would swallow the doctrine in every case. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1018 (Fed. Cir. 2006). In this regard, the Federal Circuit has specifically recognized that proposed limitations on access to the doctrine of equivalents must be applied with care, lest the equivalence analysis be improperly collapsed into a repeat of the literal infringement analysis. *Ethicon Endo-Surgery, Inc. v. U.S. Surgical Corp.*, 149 F.3d 1309, 1317 (Fed. Cir. 1998).

c. The Court's Claim Construction Does Not Bar Access to the Doctrine of Equivalents

It necessarily follows from the foregoing that the legal act of construing the claims in light of the patent specification cannot alone bar access to the doctrine of equivalents. Although the literal scope of a patent claim may be interpreted by such a construction to be more limited than it might appear at first reading, the resulting scope of the claim does not automatically justify a finding of disavowal of subject matter outside the literal scope of the construed claims. *See*, *e.g.*, *Abraxis*, 467 F.3d at 1376-77, 1382 (specification's definition of "edetate" narrowed the literal scope of the claims but did not bar application of the doctrine of equivalents); *U.S. Phillips Corp. v. Iwasaki Elec. Co.*, 505 F.3d 1371, 1378 (Fed. Cir. 2007) (specification text resulted in claim narrowed to numeric range but resort to doctrine of equivalents was not foreclosed); *Pozen*, 696 F.3d at 1169-71 (language in specification limiting literal scope of invention to range of "at least 90%, and preferably greater than 95%" did not foreclose application of the doctrine of equivalents to reach product containing 85% of the specified

ingredient). Precluding proof of equivalence based on bare definitional statements in the specification alone would result in the circular logic forbidden by the Federal Circuit, because application of the doctrine of equivalents would be reduced to "nothing more than a repeated analysis of literal infringement." *Ethicon Endo-Surgery*, 149 F.3d at 1317; *see also Deere & Co. v. Bush Hog, LLC*, Nos. 2011-1629, -1630, -1631, 2012 WL 6013405, at *5 (Fed. Cir. Dec. 4, 2012). In this regard, "exclusion" of subject matter from the description of the invention, in the sense of being "not included" by operation of the words used originally to describe the invention, is not synonymous with "disavowal" of the possible equivalence of the excluded subject matter. More is required for disavowal, as the above-cited cases make clear. (*See also* § II.B.7.b. and c.)

2. The Law Does Not Require Speculation About Untested, Theoretical Possibilities

a. The Patent Law Limits the Permissible Scope of the Disclosure

Watson contends its infringement should be excused because Plaintiffs should have *disclosed* the invention more broadly by including within the scope of the patent classes of unmade and untested salts. That contention conflicts with the substantive patent law. The patent statute, 35 U.S.C. § 112, first paragraph, imposes severe requirements on the quality of the patent disclosure. Specifically, the law requires an enabling disclosure to be provided for the *full scope* of the issued claims. *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004). Thus, the broader the scope of the patent claim is, the broader the enabling disclosure must be. Claiming an invention so broadly that it encompasses things that are not enabled, leads to invalidity of the patent, and this is a particular problem in unpredictable technologies. *See*, *id*. at 1256-57 (claim encompassing both murine and chimeric antibodies invalid where murine antibodies were enabled but chimeric antibodies were not). The effect of this statutory provision is to discourage patent applicants in unpredictable arts, like chemistry, from disclosing

embodiments they have not yet made and which may not work. Patent claims purportedly covering many such speculative embodiments have been struck down in the chemical fields for violating this disclosure provision. *See*, *e.g.*, *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1360-62 (Fed. Cir. 2007) (generic claim invalid where enabled for dicot plants but not monocot plants); *In re Vaeck*, 947 F.2d 488, 495-96 (Fed. Cir. 1991) (generic claim invalid where enabled for some but not all bacteria). Thus, this Court should not accept any contention that the patent law requires disclosure of embodiments of an invention that have not been made and that might not work as the price for securing the full measure of protection the patent law otherwise affords.

b. Salt Formation Was Unpredictable

Witnesses from both sides, including Dr. Morris (Tr. at 968:3-969:22), acknowledged that the question of whether a particular salt of an organic pharmaceutical ingredient will form and, if so, what its properties will be is fundamentally unpredictable in advance of carrying out the experiment. (Tr. at 192:17-193:1, 425:4-426:14, 432:8-434:3; PPFF at ¶ 61; *see also* PTX-580 at 1 ("Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound.").) Such experiments involve the use of scientific intuition. (Tr. at 432:8-434:3.) A substantial number of experiments may be required even during otherwise routine experimentation, and sometimes substantial difficulties are encountered. For example, the type of salt formed was well known to affect the critical solubility properties of the product. (PTX-1231 at 6665.) At least as early as 1986, the unpredictability involved in this process led some companies, and some courts, to view the results of such salt formation experiments as yielding separately patentable, unobvious results. *See*, *e.g.*, *Pfizer Inc. v. Apotex Corp.*, No. 03C 5289 (N.D. Ill. Jan. 18, 2006), *rev'd*, 480 F.3d 1348 (Fed. Cir. 2007) ("There is no reliable way of predicting the influence of a particular salt

species on the behavior of a parent compound.") (quoting *Bench Order Tr.* 23:3-6, No. 03C 5289 (N.D. Ill. Jan 18, 2006)).

In 2007, the Federal Circuit reversed course on this issue. *Pfizer Inc. v. Apotex Corp.*, 480 F.3d 1348 (Fed. Cir. 2007). In doing so, the Federal Circuit acknowledged the scientific reality of unpredictability, stating "[w]e cannot reject the district court's finding that in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be," *id*. at 1364, but concluded that such salts as *could* be made by routine experimentation should nonetheless be viewed as obvious and unpatentable, *id*. at 1366 ("Although we recognize some degree of unpredictability of salt formation . . . the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious.").

The continuing problem for patent applicants, however, is that it is impossible to know in advance without actually doing the experiment which pharmaceutical salts can be made by routine experimentation and are thus adequately disclosed and which ones cannot. The reality of the danger here is highlighted by Watson's and Egis's challenges to the validity of the hugely valuable claims of the '314 patent for alleged failure to describe how to make a crystalline calcium salt (PPFF at ¶ 62), even where calcium was specifically described in the patent. Fortunately, the subsequently developed evidence showed that the course of experimentation required to make a crystalline calcium salt was not undue. (Tr. at 415:2-13, 428:18-429:15.) Had Plaintiffs attempted to claim speculative and untested embodiments of the invention even more broadly, as Watson apparently now contends they should have, it is crystal clear from the conduct of Watson and Egis (before the Court held Watson's challenge barred and Egis dismissed the claims at trial) that Plaintiffs would have faced in this litigation not one but a

whole variety of validity challenges for failure to enable preparation of a wide variety of untested salts.

The evidence here reveals a rich record of success in finding appropriate pharmaceutically acceptable salts of the alkali (e.g., sodium and potassium) and alkaline earth (e.g., calcium and magnesium) metals, which in the aggregate account for virtually all of the internal medicines sold today in metal salt form. (§ II.B.3., *infra*.) Thus, there would have been little risk involved in positing the suitability of such salts for rosuvastatin based on actual synthesis of an example of each (patent Examples 1 and 7).[1] The record is equally rich that there was no similar body of experience for zinc (§ II.B.4., *infra*), whereby the successful outcome of a rosuvastatin zinc salt-forming experiment, even if anybody had thought about it, would have been less clear-cut in 1991. That a few companies bold enough to speculate about the operability of untested zinc and aluminum statin salts were willing to risk doing so (§ II.B.4.c., *infra*) does not mean that loss of substantial property rights should befall those, like Plaintiffs, who disclosed and claimed the types of metal salts they had actually made.

3. The ’314 Patent Disclosure Was Not Clearly Limited But Rather Disclosed Salts that Broadly Covered the Real-World, Practical Universe of Rosuvastatin Metal Salts in 1991

Watson contends that the description of useable metal salts in the ’314 patent is so sharply restricted that a person of ordinary skill in the art reading the application in 1991 would be driven to the conclusion that rosuvastatin zinc had been considered by the inventors and consciously excluded from the invention. The contention is belied by the evidence of what was

[1] Shionogi had also made some salts of rosuvastatin in the ammonium class and, therefore, also disclosed and claimed “ammonium” salts of rosuvastatin. (*See*, *e.g.*, PTX-527-T.) The Court ultimately held that the disclosure was limited to unsubstituted ammonium ions in what it acknowledged was a close question. (*See* § II.B.3., *infra*.)

happening in the real world of statin drug discovery in 1991. The literal scope of the '314 patent claims as construed by the Court in this case is, as a practical matter, quite broad.

The evidence showed that the metal ions actually used to form statin salts prior to 1991 were almost entirely restricted to the alkali and alkaline earth metal cations described in the '314 patent, as reflected by Dr. Roush's literature review. (Tr. at 545:4-572:13; AZD-5.10; AZD-5.11; AZD-5.12; *see also* PPFF at ¶¶ 40-44). That review demonstrated that the alkali and alkaline earth metal salts described in the '314 patent account for more than 99% of the 428 metal statin salts that were actually reported as having been made in the 38 prior art statin patents and printed publications in this record. The lone exception was two aluminum salts described as having been prepared in U.S. Patent No. 4,701,448 filed in 1986. (PTX-802.) By 1988, however, it had been reported that aluminum was toxic and had been associated with Alzheimer's Disease. (Tr. at 1054:1-1055:17; PTX-1433 at col. 3, ll. 19-23.)

Dr. Roush testified without contradiction that the statins on sale or in commercial development in 1991 in salt form were all alkali or alkaline earth metal salts, and that the first report in the literature of the preparation of a zinc salt of a statin did not appear until 1994. (Tr. at 562:3-18, 583:18-585:12; PTX-455; *see also* PPFF at ¶¶ 74.) Further supporting the conclusion that the alkali and alkaline earth metals disclosed and claimed in the '314 patent encompassed the universe of real-world options for metallic counterions used for oral medications like statins, the *Paulekuhn* study reported that *all* of the oral medications listed in the FDA's Orange Book and approved in the form of metal salts by the FDA from before 1982 through 2006 used alkali or alkaline earth metal ions. (PTX-1231 at 6668-69.)

In view of the foregoing, it is clear that the '314 patent adopted a *broad* description of useable metal salts, not a narrow one as Watson would have the Court conclude. A person of

ordinary skill in the art, therefore, would not find the description of pharmaceutically acceptable cations in the '314 patent to be unnecessarily or unduly limited in a way that would support a finding that an implied consideration and exclusion of unnamed cations, including zinc, was intended. Indeed, the list of metal salt-forming ions in the '314 patent is exactly what a medicinal discovery chemist of ordinary skill in the statin field in 1991 would have expected to see.

At trial, Watson attempted to make much of the fact that there were theoretically a large number of substituted ammonium ion salts that were not disclosed in the patent based on the Court's narrow construction of the term "ammonium ion." (*See*, *e.g.*, Tr. at 729:14-730:5, 734:11-22, 735:7-736:5, 740:10-741:1.) In the claim construction process, Plaintiffs had urged that the term "ammonium ion" in the '314 patent specification should be read, consistent with the parallel disclosures of "alkali metal ion" and "alkaline earth metal ion," as a generic term, in keeping with such generic usage in the prior art. (*See*, *e.g.*, PTX-1214 at p. 8, ll. 21-34; PTX-1218 at col. 2, ll. 4-12; D.I. 127 at 17-19.) Plaintiffs noted in this regard that Shionogi had actually made such substituted ammonium ions. (PTX-527-T.) Indeed, the *Berge* list of known salt formers included *only* substituted ammonium ions. (PTX-580 at 2.) The Court concluded the term meant an *unsubstituted* ammonium ion, but characterized the issue as a close question and as *not* resulting in disavowal of substituted ammonium ions. (D.I. 214 at 10.) There was thus no clear and unambiguous disavowal of substituted ammonium ions in the specification. More significantly, however, Watson is not using a substituted ammonium salt, it is using a metal salt. And the disclosure of metal salts in the '314 patent was not unduly limited for reasons noted above.

4. Rosuvastatin Zinc Was Not "Foreseeable" as a Real-World, Practical Alternative

Watson also contends that rosuvastatin zinc was so clearly identified as a viable alternative in the prior art that failure to include it in the disclosure also manifests a conscious consideration and exclusion of it. Again, the evidence is to the contrary; it showed that in the real-world of 1991, zinc was *not* viewed as a real, viable salt-forming counterion for orally administered internal medicines like statins.

a. The Experience of the Parties Confirms that Zinc Was Not a Real Alternative

Egis's Dr. Morovjan admitted that before "becoming aware of the rosuvastatin zinc project," he did not have "any experience either as a scientist or working in the intellectual property department with zinc salts of pharmaceutical ingredients." (Tr. at 478:23-479:4.) Nigel Taylor, an AstraZeneca scientist who has 27 years of drug development experience within three major pharmaceutical companies, testified that he had no personal experience with making zinc salts and never observed anyone making a zinc salt of a pharmaceutical compound. (Tr. at 149:17-150:4.) More specifically with regard to rosuvastatin itself, Yasuo Ida, a long-time scientist at Shionogi who, as Shionogi's Rule 30(b)(6) witness, studied the '314 patent inventors' notebooks and reports, testified that he could not find any evidence in the Shionogi documents that Shionogi had ever considered a zinc salt of rosuvastatin during development of the compound. (Tr. at 318:15-319:10.)

The documentary evidence is in accord. Nigel Taylor identified three "counterion lists" that were developed by researchers at AstraZeneca as a guide for salt selection. (*See* Tr. at 150:5-17, 151:11-15, 153:10-157:24; PTX-1329; PTX-1330; PTX-1331.) Zinc did not make the first two lists. (PTX-1329; PTX-1331.) When zinc finally made it onto the AstraZeneca counterion list in 2004, it was accompanied by the cautionary text: "Used as a dietary

supplement. Little or no data in relation to use in salt formation – class 3." (PTX-1330 at AZW1014168, AZW1014190.)

b. The Scientific Literature Confirms that Zinc Was Not a Real Alternative

Public and private literature surveys are in accord with the perception that zinc was not a realistic, viable salt-forming counterion for use in internal medicines. Dr. Roush reviewed the literature underlying the 1977 *Berge* publication and concluded that virtually all of the zinc-containing pharmaceutical products marketed prior to 1991 were either topical preparations, like dandruff shampoo, or dietary supplements where zinc was the active ingredient, not internal medicines containing zinc salts. (Tr. at 578:13-579:18; PTX-580; PTX-1198.) When Egis evaluated the situation in 2010, it concluded that there were no commercial internal medicines containing zinc salts. (Tr. at 489:18-491:3; PTX-460 at W214168.) When Paulekuhn et al. reviewed the approved drug products listed in FDA's Orange Book, they concluded that none of the metal salts of the oral medications approved from before 1982 through 2006 were formed with zinc metal ions. (PTX-1231 at 6668-69.) Simply put, zinc was seldom, if ever, used to prepare salts of drugs for internal pharmaceutical use.

Published handbooks also confirm the obscurity of zinc as a salt-forming ion. As late as 2002, The Handbook of Pharmaceutical Salts mentions zinc among "Class 3" or a third-choice class of counterions. (PTX-1412 at 345.) The handbook's classification represents a descending preference for salt forms. The first class salt-formers are "those of unrestricted use for that purpose . . . ." (*Id*. at 331.) The usual alkali and alkaline earth metal ions are included in Class 1. (*Id*. at 345.) The third class, to which zinc is relegated, the last in the handbook's classification system, "might be interesting under particular circumstances . . . . Some of them are assigned to this class because they have their own pharmacological activity. Also, some of

the acids and bases were used much less frequently in the past." (*Id*. at 332; *see also* Tr. at 585:13-590:21.)

c. Speculative Inclusion of Zinc in Patents for Products that Never Used Zinc Did Not Alter the Scientific Real World

The inclusion of zinc in speculative laundry lists of increasingly bizarre salts that might be tried for other statins adopted by a few statin manufacturers did not make rosuvastatin zinc a real-world, foreseeable alternative. Nobody had made such a zinc salt as of 1991 for any statin. What the properties of any such salt would be, and how the properties of a rosuvastatin zinc salt would compare to the zinc salts of other statins, were then unknown and unpredictable.

Those speculative lists always included zinc along with aluminum, which was known to be toxic by 1988 (PTX-1433 at col. 3, ll. 19-25; PPFF at ¶ 58), and sometimes included zinc with even more obscure metals, like cobalt, nickel, and iron (*e.g.*, PTX-801 at col. 3, ll. 25-29; PTX-802 at col. 2, ll. 50-55; PTX-806 at col. 7, ll. 1-5), that had apparently never been used in pharmaceutical salts for internal use (PTX-484; PTX-580; PTX-1231). The fact that nobody developed a zinc statin, or any zinc salt of an FDA-approved internal medicine from before 1982 through 2006 (PTX-1231), strongly demonstrates that the speculation upon which Watson relies was recognized as such and ignored by actual people of ordinary skill in the art.[2]

The Federal Circuit's predecessor expressed skepticism about the significance and importance of references in patents to speculative alternatives that were never actually pursued. In *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978), for example, the court emphasized that "[i]n determining how the [prior art] disclosure was interpreted by those skilled in the art, we are more

[2] Although Watson introduced in evidence a number of Shionogi patents from other inventors that arguably generically encompassed zinc salts, none of those patents specifically listed zinc as a pharmaceutical salt-forming cation, disclosed working examples of zinc salts specifically, or concerned rosuvastatin or any other statin compound. (Tr. at 743:9-745:12; DTX-700; DTX-701; DTX-702; DTX-703.) A person of ordinary skill in the art would not, therefore, view those other patents as disclosing appropriate salts for rosuvastatin.

impressed by what those so skilled Did than by what they Said," particularly where "speculative statements" in prior art patents were "recognized as such and ignored by those working in the art."

d. Egis and Watson Treated Rosuvastatin Zinc as Unforeseen

Beyond the foregoing, Watson's licensor and partner (PTX-45; PTX-46; PPFF at ¶ 160), Egis, treated rosuvastatin zinc as unforeseeable in prosecuting patent applications on it around the world. More specifically, Egis applied for a patent on rosuvastatin zinc in which it argued to the PTO and the EPO that rosuvastatin zinc was novel. (*See* PTX-30 at W165141.) This was sufficiently significant to Watson that Watson reported it to the FDA in Watson's regulatory filings. (PTX-16 at W1282.) Indeed, under its Commercialization and Supply Agreement with Egis, Watson was not only to be licensed under any patent issued to Egis for rosuvastatin zinc but also was to benefit from the exclusive rights that would flow from those issued patents. (PTX-45 at W17595, W17615.) Thus, Watson as well as Egis stood to benefit financially from Egis's arguments to the PTO and the EPO, and Watson should not now be heard to allege a contrary state of fact as to the foreseeability of rosuvastatin zinc.

In particular, Egis strenuously argued before the PTO that rosuvastatin zinc was a novel composition of matter:

> The reference discloses no example for the preparation of any form of rosuvastatin, and certainly no preparation of rosuvastatin zinc. . . . The reference simply treats rosuvastatin or its metal salts as known, available starting materials.
>
> Such a disclosure is nothing more than mere speculation as to the existence of rosuvastatin zinc salts and merely naming zinc salts of rosuvastatin in WO 2005/123082 as a possible active pharmaceutical ingredient in the compositions does not amount to anticipation of rosuvastatin without something more. In order for the reference to be anticipatory, the reference would need to either provide an example for the preparation of rosuvastatin zinc, or at the very least provide in the description of the invention a process

> for preparing the rosuvastatin zinc from known starting materials that would have enabled one skilled in the art to prepare zinc rosuvastatin without the need to carry out undue experimentation.

(PTX-1302 at AZW1015615.) In seeking patents around the world, Egis also argued that rosuvastatin zinc was nonobvious:

> Therefore the person skilled in the art would not consider zinc as an alternative to alkaline earth metals and alkaline [sic] metals since difficulties due to complexation are expected.

(PTX-1301 at AZW1014498.)

In prosecuting its patent applications, Egis specifically dismissed the pertinence of suggestions to make zinc salts of *other* statins, like those upon which Watson now principally relies. With regard to WO 2006/017698, for example, Egis argued that the disclosure of the actual preparation of *pravastatin* zinc did not make *rosuvastatin* zinc foreseeably obvious:

> Pravastatin, however, has significantly different chemical structure than rosuvastatin. In pravastatin, no nitrogen atoms possessing strong complexing behavior . . . are present. Therefore, it is not obvious for the person skilled in the art and having knowledge about pravastatin zinc salt to attempt the synthesis of rosuvastatin zinc (2:1) salt with reasonable hope of success.

(*Id*. at AZW1014499.)

Mr. Zsigmond testified that Egis filed patent applications only on subject matter it viewed as novel and nonobvious. (Tr. at 342:1-9.) Dr. Morovjan summarized Egis's views in a March 26, 2010, memorandum, which states: "The state of the art is silent about methods suitable for the preparation of zinc salts of statins, thus the skilled person would have to face a significant burden of experimentation without reasonable expectation of success." (PTX-460 at W214169.) Dr. Morovjan's and Egis's assertions regarding the unforeseeability of a rosuvastatin zinc salt are fully supported by Watson's expert, Dr. Morris. At trial, Dr. Morris testified that "it is

impossible to know without performing these experiments whether these remaining rosuvastatin salts would be formed." (Tr. at 968:7-20.)

The actions of Watson's predecessor, Arrow, upon learning of rosuvastatin zinc, confirm that zinc salts were not a common, real-world alternative as recently as 2008. (PTX-108; PTX-512; PTX-513.) Within weeks of Arrow's initial contact with Egis regarding the possibility of early entry into the rosuvastatin market with rosuvastatin zinc, Arrow's North American affiliate, Cobalt, requested an outside evaluation of the safety of administering a drug in the form of a zinc salt. (PTX-512; PTX-513.)

This constellation of evidence from a variety of sources converges to demonstrate that rosuvastatin zinc was not a realistically foreseeable alternative in 1991.

5. Watson's Reliance on the Alleged "Foreseeability" of Rosuvastatin Zinc is Misplaced

a. "Foreseeability" Alone Cannot Bar Access to the Doctrine of Equivalents

Watson's allegations depend heavily on the alleged "foreseeability" of a rosuvastatin zinc salt. Yet, "foreseeability" of an alleged equivalent cannot possibly alone bar access to the doctrine of equivalents. In both *Graver Tank* and *Warner-Jenkinson*, the Supreme Court cited known interchangeability of the equivalent in the prior art as a factor *supporting* a finding of infringement, not as barring access to the doctrine. *Graver Tank*, 339 U.S. at 607; *Warner-Jenkinson*, 520 U.S. at 36-37. To the extent that more recent panel opinions of the Federal Circuit have discussed foreseeability in other contexts relating to the doctrine of equivalents, they cannot be read as barring resort to the doctrine based solely on foreseeability in view of this contrary Supreme Court authority. (*See* § II.B.5.b., *infra*.)

The proper role for the foreseeability inquiry, according to the Supreme Court, lies in application of the doctrine of "prosecution history estoppel." *See Festo Corp. v. Shoketsu*

Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 733-34 (2002). Such an estoppel may arise where a patent applicant originally presented claims broad enough to cover the alleged equivalent but narrowed the claims to exclude the alleged equivalent for some reason related to patentability. In that context, not present here because the scope of the claimed salts was never altered by amendment (§ II.E.1.; *see also* PPFF at ¶¶ 25-35), the burden would be upon the patentee to explain why the doctrine of equivalents should nonetheless apply. In 2002, the Supreme Court suggested that "unforeseeability" of the alleged equivalent at the time of the narrowing amendment might provide a justification for avoiding what would otherwise have been a prosecution history estoppel. *Festo*, 535 U.S. at 738.

The Federal Circuit has at times applied this "foreseeability" standard quite severely in the prosecution history estoppel context under circumstances profoundly different from those presented here. In the usual prosecution history estoppel case, presentation of a narrowing amendment is viewed as triggering in the mind of the patent applicant consideration of what it is that he had previously claimed that he is now giving up. *See*, *e.g.*, *Festo*, 535 U.S. at 734-35. Under such circumstances, a decision to give up claimed "foreseeable" alternatives will normally lead the court to apply prosecution history estoppel and leave the patentee with the narrowed scope of protection.

There is no such triggering event associated with simply filing an original patent application. The Supreme Court itself has recognized that the situation posed by including a limiting phrase in an original patent claim is "very different" from an amendment adopting a narrower phrase in place of originally presented broader language. *See*, *e.g.*, *Warner-Jenkinson*, 520 U.S. at 31. All Plaintiffs did here was include a limiting phrase in the text of an original application that referred to the classes of salts they had actually made.

Such prosecution history estoppel cases are thus a far cry from requiring a patent applicant either to make and test additional embodiments of his invention prior to filing an original patent application, or to speculate at his peril about the suitability of unmade additional embodiments of his invention in an unpredictable art simply because an adverse litigant may allege years later that they might have been "foreseen."

b. The Lack of Real-World Foreseeability Supports Access to the Doctrine of Equivalents

In complex pharmaceutical arts, where the "foreseeability" of an alleged equivalent is not so readily apparent, the Federal Circuit often has found infringement under the doctrine of equivalents. For example, in *Abraxis* the claimed emulsion containing propofol and disodium edetate (EDTA) did not literally include structural analogs like "DTPA" because the "edetate" term was held to be narrowly defined in the specification. 467 F.3d at 1376-77. Yet, the infringer's use of such structural analogs was nonetheless found to be an insubstantial change under the doctrine of equivalents. *Id*. at 1382. The court was influenced by the fact that the accused infringer had specifically chosen the DTPA analog because of its structural similarity to EDTA, and had sought a substitute that would match the patent owner's FDA-approved EDTA drug product and would thus be approvable as a generic equivalent by the FDA. *Id*. at 1381.

Here, Watson and Egis obviously chose a zinc salt of rosuvastatin because of zinc's chemical similarity to the calcium found in the Plaintiffs' Crestor® product, and the similarity of its interaction with the active organic portion of the rosuvastatin molecule, in the hope that rosuvastatin zinc would be approved as bioequivalent to Crestor® by the FDA. (*See*, *e.g.*, Tr. at 663:13-20; PTX-17 at W1452; PTX-18 at W1595; PTX-334 at W173641, W173652-53; PTX-1254; PTX-1294; *see generally*, § II.A., *supra*.)

Moreover, the accused infringer in *Abraxis* was found to have treated DTPA as unforeseeable by prosecuting its own patent application on the composition. *Abraxis*, 467 F.3d at 1381-82. The same is true here. As set forth extensively in § II.B.4.d., *supra*, Watson's licensor and partner, Egis, separately applied for patents on rosuvastatin zinc, arguing that zinc was novel and not a foreseeable or obvious invention. These admissions by Egis, and the supportive admissions of Watson's expert at trial (Tr. at 968:3-969:22, 1065:18-1066:10), confirm their view that development of a rosuvastatin zinc salt would have been unpredictable in 1991, and that the speculative disclosure of a theoretical zinc salt of some other statin compound did not suggest the suitability or even the foreseeability of a zinc salt of rosuvastatin. The ability to form a rosuvastatin zinc salt and the resulting properties of any such salt having been repeatedly characterized by Watson's partner and witnesses as unpredictable, it is clear that this case is much more like *Abraxis*, where access to the doctrine of equivalents was permitted, than *Sage Prods. Inc. v. Devon Indus., Inc.*, 126 F.3d 1420 (Fed. Cir. 1997), where access was denied.

Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC, 683 F.3d 1356 (Fed. Cir. 2012), is not to the contrary. *Wrigley* involved a simple mixture of ingredients, not the unpredictable product of a new chemical reaction involved here. *See*, *e.g.*, *In re Corr*, 347 F.2d 578, 580 (CCPA 1965) ("[W]e are apparently not faced with the problem of unpredictability due to chemical reactions" in mixture of materials.). In that mixture, a selected cooling agent, said to bear a structural resemblance to menthol, was described as yielding unexpected results. *Wrigley*, 683 F.3d at 1366. The alleged equivalent did not bear the required structural similarity to menthol and was not described in the patent as yielding the same unexpected result. *Id*. These factors alone would have warranted the court's finding of no equivalence in fact.

The court nonetheless further noted that the alleged equivalent had been disclosed to the inventors at the same time as the claimed material and that both had been disclosed as being appropriate for the same uses. *Id*. This observation by the *Wrigley* panel cannot be read as barring access to the doctrine of equivalents simply because the equivalent was known in the prior art. The Supreme Court has twice cited the known interchangeability of the equivalent in the prior art as supporting a finding of infringement under the doctrine of equivalents, not as barring its application. *Graver Tank*, 339 U.S. at 607; *Warner-Jenkinson*, 520 U.S. at 36-37.

At most, such consideration of the equivalent by the inventor may be relevant to whether there are substantial differences between the claimed invention and the alleged equivalent, as it was in *Tanabe Seiyaku Co. v. U.S. Int'l Trade Comm'n*, 109 F.3d 726, 733 (Fed. Cir. 1997). There, evidence that the patent owner had tried and failed to use the material later alleged to be an equivalent was cited as evidence that there were in fact substantial differences between the claimed invention and the alleged equivalent. That the patentee in *Wrigley*, with two concrete, real-world options with known properties before him, chose one but not both of these alternatives for inclusion in the patented mixture is some evidence that they were not in fact equivalent, particularly where the excluded embodiment lacked the required structural similarity to menthol. As noted extensively above, in the present case, rosuvastatin zinc was not a concrete, real-world alternative with known properties in 1991.

c. The Inventors Did Not Make, Use, or Evaluate Zinc Salts of Rosuvastatin

At closing arguments, the Court asked why the inventors did not disclose the salts more broadly. As a preliminary matter, it must be noted that unlike the inequitable conduct issue presented in the prior Crestor® litigation that turned on subjective intent, the question of explicit or implicit disavowal at issue here is an objective inquiry based on the patent, its prosecution

history, the state of the prior art, and the perceptions of scientists of ordinary skill in the statin art as of the 1991 effective filing date of the '314 patent. *Abraxis*, 467 F.3d at 1381-82 (disavowal judged from perspective of person of ordinary skill in the art reading the patent).

Nonetheless, the overwhelming weight of the evidence here indicates that nobody ever perceived any deficiencies in the disclosure of useable salts in the '314 patent. Nor should they have. The alkali and alkaline earth metal salts were, as a practical matter, the only metal salts that had ever been made or sold in the statin field, one of each had been successfully made by the inventors, and these classes were disclosed and claimed in the patent.

There is no evidence that the '314 patent inventors made, used, or evaluated zinc salts of rosuvastatin. The inventors' laboratory notebooks and summary reports of their work were introduced into evidence. (*See*, *e.g.*, PTX-340-T; PTX-341-T; PTX-526-T; PTX-527-T; PTX-531-T; PTX-532-T; *see also* PPFF at ¶ 71.) Nowhere in that record is there any mention of zinc salts generally or zinc salts of rosuvastatin specifically. (*See also* PPFF at ¶¶ 71-72.) Indeed, there is no evidence that anybody, anywhere ever even considered the possibility of a rosuvastatin zinc salt until it was mentioned in a Chinese patent application filed in 2004. (PTX-1301 at AZW1014501-25; PTX-1302 at AZW1015584-604.) That Shionogi never evaluated a rosuvastatin zinc salt or any other rosuvastatin transition metal salt is entirely reasonable on this record, as confirmed by the fact that another sophisticated pharmaceutical company, AstraZeneca, likewise never considered the possibility of a rosuvastatin zinc salt in its investigation of alternative rosuvastatin salts. (Tr. at 149:17-150:4; *see also* PTX-564; DTX-724.)

Significantly, the application for the '314 patent was the *second* statin patent application these inventors had filed, and the first application had described and claimed suitable salts

exactly the same way. (PTX-751 at col. 2, ll. 47-49 and claim 1.) There is no evidence of a considered rejection of other types of rosuvastatin salts. Knowing the state of the art, the enumerated metal salts in the disclosure were exactly what a skilled medicinal discovery chemist working in the statin field in 1991 would have expected to see.

6. Watson's Reliance on *Sage Products* is Misplaced

With no case directly in support of its position, Watson heavily relies on an alleged implicit disavowal of all rosuvastatin salts not literally covered by the '314 patent claims based on *Sage Products* and its progeny. Those cases are inapplicable here.

Sage Products involved a predictable technology. In contrast to the disclosure requirements in unpredictable arts, like that involved here, a quite different disclosure rule applies in predictable technologies, such as mechanical cases. As the Federal Circuit noted in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533 (Fed. Cir. 1987), "[i]f an invention pertains to an art where the results are predictable, e.g., mechanical as opposed to chemical arts, a broad claim can be enabled by disclosure of a single embodiment . . . ." Herein lies a fundamental and important distinction between the present case and *Sage Products*.

Sage Products involved a simple mechanical device that was claimed exceptionally narrowly. Indeed, critical to the holding in *Sage Products* was the recognition that the disclosed device could have been *claimed* more broadly without outdistancing its disclosure or running afoul of the disclosure requirements of the patent statute. The court in *Sage Products* held: "If Sage desired broad patent protection for any container that performed a function similar to its claimed container, *it could have sought claims with fewer structural encumbrances*." 126 F.3d at 1425 (emphasis added). Here, in stark contrast, in a more unpredictable technology, the rosuvastatin salts were claimed broadly. Indeed, they were claimed as broadly as the work that had been done and the written description of the invention permitted.

Moreover, the public harm sought to be prevented in *Sage Products* is not present here: "Had Sage done so [and claimed its invention more broadly], then the Patent and Trademark Office (PTO) could have fulfilled its statutory role in helping ensure that exclusive rights issue only to those who have, in fact, contributed something new, useful, and unobvious. Instead, Sage left the PTO with manifestly limited claims that it now seeks to expand through the doctrine of equivalents." *Id*. While the court noted that Sage had avoided PTO examination of the patentability of the broad subject matter alleged to infringe under the doctrine of equivalents, the prosecution history of the '314 patent here unambiguously established that the novelty and nonobviousness of the salts claimed in the '314 patent reside in the rosuvastatin anion portion of the molecule, not the particular positively charged ion used to form the salt. (PTX-741; PTX-1317; *see also* PPFF at ¶¶ 20-24.) There is no risk in this case that the alleged equivalent does not embody the novel and nonobvious features of the '314 patent invention.

Finally, *Sage Products* has been narrowly construed; it is hardly the touchstone for the creation of new law. Since *Sage Products* and other similar decisions, the Federal Circuit has been careful to explain that those cases involved peculiar facts where no reasonable jury could find the alleged equivalent to have been insubstantially different from the claimed invention. *See DePuy Spine*, 469 F.3d at 1017-18; *Deere & Co.*, 2012 WL 6013405, at *4. In sharp contrast, here equivalence in fact has been amply proven. As the Federal Circuit later observed in *Ethicon Endo-Surgery*, 149 F.3d at 1318, *Sage Products* and similar cases "were decided on their facts" and "did not read the doctrine of equivalents out of existence when a claim limitation is not expressly met by an accused device."

7. There Is No Evidence to Support Any Recognized Legal Theories To Excuse Watson's Infringement in this Case

a. There Was No Prosecution History Estoppel

Prosecution history estoppel is not applicable here because the originally presented specification and claims, as the Court has now construed them, never encompassed zinc salts and the claim language describing rosuvastatin salts was never amended or otherwise narrowed through argument—at reissue or otherwise—to exclude rosuvastatin zinc or any other rosuvastatin salt. (PPFF at ¶¶ 25-35, summarizing prosecution history.) The scope of the claimed rosuvastatin salts was left untouched by the claim amendments during prosecution. (*Id*.) Thus, the doctrine of equivalents is still available to prove infringement in this case.

Even where a narrowing amendment or argument has been made, *Festo* provides that the estoppel may nonetheless be avoided if the rationale underlying the amendment bears "no more than a tangential relation to the equivalent in question." 535 U.S. at 740. Here, the rejections made during patent procurement had nothing to do with either the novelty or nonobviousness of any rosuvastatin salt or with which cations were within the scope of the claims. (PTX-741; PTX-1317; PPFF at ¶¶ 22, 28, 32, 34.) Such claim amendments as there were, therefore, bore no more than a tangential relationship to the rosuvastatin zinc salt here at issue and do not foreclose Plaintiffs' reliance on the doctrine of equivalents.

b. There Was No Express Disavowal of Rosuvastatin Zinc in the '314 Patent

In certain circumstances, courts have held that clear statements in the text of the patent stating what the invention *is NOT* may bar proof of infringement under the doctrine of equivalents where those statements specifically distinguish the invention from what is later alleged to be an equivalent. Examples of such cases include *AstraZeneca AB v. Mutual Pharmaceutical, Co.*, 384 F.3d 1333, 1340 (Fed. Cir. 2004) (alleged equivalent criticized as

potentially causing "precipitation of the drug"), and *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337, 1345 (Fed. Cir. 2001) (alleged equivalent was "specifically identified, criticized, and disclaimed").

Courts have imposed a high threshold for finding such a disavowal of an alleged equivalent. The alleged equivalent must have been "specifically excluded." *See Abbott Labs. v. Andrx Pharms., Inc.*, 473 F.3d 1196, 1211 (Fed. Cir. 2007); *Athletic Alts., Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1582 (Fed. Cir. 1996); *Ethicon Endo-Surgery*, 149 F.3d at 1317. Measured against an objective standard, any such specific exclusion must be "clear and unmistakable." *See Abraxis*, 467 F.3d at 1381 (disclaimer required proof of a "clear and unmistakable surrender"); *see also SciMed*, 242 F.3d at 1341, 1347 ("clear and binding statement to the public that metallic structures are excluded" as understood by a person skilled in the field of the invention).

There are no such clear statements of disavowal in the '314 patent. Rosuvastatin zinc was neither disclosed in the text of the '314 patent specification, nor criticized, nor distinguished from the rosuvastatin salts that are discussed in the patent. (PTX-1227.) As a result, there is no evidentiary basis to find that rosuvastatin zinc was expressly disavowed.

c. There Was No Implicit Disavowal—Rosuvastatin Zinc Is Not the "Opposite" of Salts Expressly Disclosed in the '314 Patent

Courts have found an implicit disavowal of certain classes of equivalents where the patent claims a specific form of the invention that is the "opposite" of the alleged equivalent. *See*, *e.g.*, *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 955-56 (Fed. Cir. 2006) (claim to dental implant with a "convex" abutment not infringed by implant with a "concave" abutment because claim "clearly excludes distinctly different and even opposite shapes"); *see also Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158-61 (Fed. Cir. 1998) (conically shaped artificial hip prosthesis not infringed by a hemispherically shaped device); *Planet Bingo, LLC v. Gametech Int'l, Inc.*,

472 F.3d 1338, 1345 (Fed. Cir. 2006) (theory of equivalence may be legally insufficient when the accused product contains the antithesis of the claim limitation).

Zinc is not the "opposite" of the salt-forming cations disclosed in the '314 patent and does not form a salt of rosuvastatin that is contrary to or clearly distinguishable from the literally claimed salts. Instead, as previously discussed (§ II.A.), the evidence available in 2010 and adduced at trial proves that rosuvastatin zinc is substantially the same as the claimed salts, including rosuvastatin calcium in particular, in the context of the invention of the '314 patent.

d. The "All-Limitations" Rule Is Not Implicated in this Case

A large number of cases have rejected assertions of infringement under the doctrine of equivalents because it would have completely vitiated an element of the claim. This doctrine is not applicable here because the patent claims were to rosuvastatin in the form of a pharmaceutically acceptable salt and the alleged equivalent is rosuvastatin in the form of a pharmaceutically acceptable salt. (PTX-1227 at col. 16, ll. 30-35; PTX-17 at W1451; PTX-317 at W6295-96.) One equivalent pharmaceutically acceptable metal cation has been substituted for those literally claimed. All claim elements remain present either literally or in the form of an equivalent. *See generally Deere & Co.*, 2012 WL 6013405, at *5 ("[T]he doctrine of equivalents, by definition, recognizes that an element is missing that must be supplied by the equivalent substitute. If mere observation of a missing element could satisfy the vitiation requirement, this 'exception' would swallow the rule.").

e. The '314 Patent Does Not Attempt To "Recapture" Unclaimed Matter

"[W]hen a patent drafter discloses but declines to claim subject matter, . . . this action dedicates that unclaimed subject matter to the public," and recapturing the unclaimed subject matter by resorting to the doctrine of equivalents is not permitted. *Johnson & Johnston*, 285

F.3d at 1054; *see also Maxwell*, 86 F.3d at 1106-08 (only one of two disclosed fastening means claimed). Here, rosuvastatin zinc is not disclosed in the text of the patent. Accordingly, the failure to literally claim rosuvastatin zinc, under the Court's claim construction, cannot be the basis for inferring the disavowal of rosuvastatin zinc.

The Background section of the '314 patent text cites a number of prior art publications as describing the historical development of statins. U.S. Patent No. 4,444,784 ("the '784 patent") is there cited as disclosing simvastatin, a prior art statin sold in lactone form, not in salt form. (Tr. at 558:12-15; PTX-1234; *see also* PPFF at ¶¶ 20-21.) Indeed, the '784 patent contains no actual example of the preparation of any simvastatin salt. It does, however, contain a speculative list of hypothetical simvastatin salts, including both zinc and toxic aluminum salts, buried at column 15 of the disclosure. (PTX-1234.)

The '784 patent was not cited as support for the '314 patent's disclosure of rosuvastatin salts and does not disclose rosuvastatin or any of its salts. The background reference to this disclosure of simvastatin cannot constitute an abandonment or dedication to the public of undisclosed rosuvastatin zinc salts. *See Ventana Med. Sys., Inc. v. Biogenex Labs., Inc.*, 473 F.3d 1173, 1181 (Fed. Cir. 2006) (noting that "general statements, without more, will not be interpreted to disclaim every feature of every prior art device discussed in the 'BACKGROUND ART' section of the patent."); *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 429 F.3d 1364, 1379-80 (Fed. Cir. 2005) (although the patent twice referred to microcrystalline cellulose, such references were not to microcrystalline cellulose as an alternative to the claimed element of the invention).

C. The Equities Here Support Application of the Doctrine of Equivalents

1. Application of the Doctrine of Equivalents Is Fundamentally Equitable To Protect the Patent Holder and Depends on the Unique Facts of Each Case

The doctrine of equivalents has been applied as an adjunct to the provisions of the U.S. patent statute for more than 150 years. The problem the doctrine is intended to address was extensively explained by the Supreme Court in *Graver Tank*, 339 U.S. at 607:

> [C]ourts have also recognized that to permit imitation of a patented invention which does not copy every literal detail would be to convert the protection of the patent grant into a hollow and useless thing. Such a limitation would leave room for—indeed encourage—the unscrupulous copyist to make unimportant and insubstantial changes and substitutions in the patent which, though adding nothing, would be enough to take the copied matter outside the claim, and hence outside the reach of law. . . . To prohibit no other would place the inventor at the mercy of verbalism and would be subordinating substance to form.

Application of the doctrine of equivalents has historically been recognized as fundamentally equitable in nature. *See, e.g.*, *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 805 F.2d 1558, 1572 (Fed. Cir. 1986) ("The doctrine of equivalents . . . exists solely for the equitable purpose of 'prevent[ing] an infringer from stealing the benefit of an invention,'" quoting *Graver Tank*, 339 U.S. at 608); *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1538 (Fed. Cir. 1991) (describing doctrine of equivalents as an "equitable doctrine"); *Int'l Visual Corp. v. Crown Metal Mfg., Co.*, 991 F.2d 768, 774 (Fed. Cir. 1993) (Lourie, J., concurring) ("In recent years, we have emphasized that the doctrine [of equivalents] is equitable in nature." (citations omitted)).

The equitable inquiry does not extend so far as to require a malevolent intent on the part of the infringer. *Warner-Jenkinson*, 520 U.S. at 37. Rather, it is intended to yield a fundamentally *fair* result, recognizing that "the doctrine of equivalents, when applied broadly,

conflicts with the definitional and public-notice functions of the statutory claiming requirement," *id*. at 29, and that "[t]he language in the patent claims may not capture every nuance of the invention or describe with complete precision the range of its novelty," and that any resulting uncertainty in the scope of the patent is "the price of ensuring the appropriate incentives for innovation." *Festo*, 535 U.S. at 723, 731 (2002). *See*, *e.g.*, *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1521 (Fed. Cir. 1995) (en banc) ("*Warner-Jenkinson I*"), *rev'd on other grounds*, 520 U.S. 17 (1997) ("Thus, in doctrine of equivalents cases, this court's allusions to equity invoke equity in its broadest sense–equity as general fairness.").

In keeping with the fundamentally equitable nature of the doctrine, its application is highly fact-specific and is based on the "totality of the circumstances of each case." *Freedman Seating*, 420 F.3d at 1359; *Claude Neon Lights, Inc. v. E. Machlett & Son*, 36 F.2d 574, 576 (2d Cir. 1929) ("other decisions have little or no value"); *Warner-Jenkinson*, 520 U.S. at 24-25, quoting *Graver Tank*, 339 U.S. at 609 ("Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum.").

2. The Invention of the '314 Patent Was Medically Important and Deserves a Broad Range of Equivalence

The range of equivalents for the '314 patent should be broad, because of the important advance the claimed invention provided patients suffering from high levels of cholesterol. "It has long been recognized that the range of permissible equivalents depends upon the extent and nature of the invention, and may be more generously interpreted for a basic invention than for a less dramatic technological advance." *Tex. Instruments*, 805 F.2d at 1563. "[C]ourts have held that the breadth of equivalents . . . depends on the degree to which the patent represents an advance over the prior art." *Hughes Aircraft Co. v. United States*, 29 Fed. Cl. 197, 209 (Fed. Cl. 1993).

Liberal treatment under the doctrine of equivalents does not hinge on characterization of the invention as a "pioneer." As the Supreme Court has noted:

> In the case before us . . . we think that Eibel made a very useful discovery, which has substantially advanced the art. His was not a pioneer patent, creating a new art; but a patent which is only an improvement on an old machine may be very meritorious, and entitled to liberal treatment.

Eibel Process Co. v. Minn. & Ont. Paper Co., 261 U.S. 45, 63 (1923); *see id*. at 69.

Here, Plaintiffs' invention substantially advanced the treatment of high levels of LDL cholesterol and the management of atherosclerosis, as Dr. Pears explained and as Watson told the FDA in its NDA filing. (Tr. at 101:21-103:2; 106:10-107:18, 115:9-123:13; PTX-1294 at W9716-21, W9727-44.) Plaintiffs' Crestor® rosuvastatin calcium substantially improved the ability to get patients to their treatment target goals, and it is the most effective statin for reducing "bad" LDL cholesterol while substantially raising "good" HDL cholesterol. (Tr. at 103:3-115:8; PTX-1594 at AZW1017294, AZW1017302, AZW1017303, AZW1017305, AZW1017307; *see also* PPFF at ¶ 16.) In addition to diet, Crestor® has been approved as a therapy to slow the progression of atherosclerosis in adult patients. (PTX-1289.) In one study, 52.1% of the patients treated with Crestor® "demonstrated an absence of disease progression . . . compared to 37.7% of patients in the placebo group." (PTX-1289 at 6.) Significantly, the scientific evidence established that rosuvastatin is not a "me-too" statin but instead has a unique additional binding interaction with the cholesterol-producing enzyme it inhibits that is not shared with any other statin. (PTX-734 at 1163.)

3. Watson and Egis Recognized the Risk of Infringement

The public notice function of patent claims was served in this case. Upon its initial reading of the text of the basic Shionogi application, Egis concluded that rosuvastatin zinc was covered as a non-toxic pharmaceutically acceptable salt. (PPFF at ¶ 162.) Even after developing

a theory on literal infringement, Egis and Watson's predecessor clearly recognized that "the possibility is not precluded that the zinc ion will be considered equivalent with calcium ion, or with even greater probability, with the magnesium ion . . . ." (PTX-458-T at W0184504-05.) Indeed, no reasonable reader of the prosecution history leading to the '314 patent could conclude that the particular metal ion chosen for salt formation, assuming the salt could be made and was soluble enough to work, was the least bit important to the novelty and nonobviousness of the invention.

4. Watson and Egis Were Not Innovators

Watson cannot wrap itself in the mantle of a true innovator for purposes of the infringement analysis. Watson's licensor and partner, Egis, was not actually the first to suggest production of a rosuvastatin zinc salt. A Chinese company, Lunan Pharmaceutical, proposed such a product and claimed it as part of its invention in a Chinese patent application filed in 2004. (PTX-1301 at AZW1014501-25; PTX-1302 at AZW1015584-604.)

5. Enforcement of the '314 Patent Against Watson's Rosuvastatin Zinc Is Fair and Reasonable

Nobody can doubt based on the prosecution history of the '314 patent that the product Watson proposes to sell embodies the novel and nonobvious aspects of Plaintiffs' patented invention. There is no evidence of gamesmanship in the way the original patent application was drafted. It used the same description of useable salts that had been used without incident in the inventors' prior statin patent application. That description disclosed the alkali and alkaline earth classes of metal salts, which the inventors had actually exemplified and which were in common use at the time. Nobody had then synthesized a zinc salt of any statin, or even considered the possibility of a rosuvastatin zinc salt until years later.

By 2010, however, when Watson undertook to file an NDA on rosuvastatin zinc, there had been a number of published reports of rosuvastatin zinc products (PTX-47-T at W47492, W47509, W47514, W47528). Watson sought to gain a windfall (three years of exclusive generic presence in the rosuvastatin marketplace) by adoption and use of this equivalent expedient that simply did not exist in the real world when the original application for the '314 patent was filed. (PPFF at ¶ 156, 158, 160.)

Plaintiffs, not Watson, discovered the unique and unobvious chemical structure of rosuvastatin, discovered its therapeutic properties, proved through years of testing that it was safe and effective for the treatment of a variety of important disease states, and established the excellent reputation the product enjoys today.

In contrast, Watson's contention underlying assertion of its right to market rosuvastatin—that Shionogi used the words "refers to" instead of "includes"—leaves the patentee here "at the mercy of verbalism and would be subordinating substance to form," contrary to the mandate of *Graver Tank*, 339 U.S. at 607.

No rule of law demands the result sought by Watson, and fundamental concepts of fairness should operate to prevent it.

III. CONCLUSION

For the reasons set forth above, in the Joint Statement of Undisputed Facts, and in Plaintiffs' Proposed Findings of Fact filed concurrently herewith, Plaintiffs respectfully request judgment that Watson has infringed claims 6, 7, and 8 of the '314 patent.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on the 25th day of January, 2013 I electronically served a true and correct copy of the foregoing PLAINTIFFS' POST-TRIAL BRIEF to the below individuals:

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